REMARKS

Applicants thank the Examiner for his time and thoughtful discussion during the telephonic interview conducted with Applicant's attorney on April 1, 2003. During the interview, the prior art rejections were discussed. The Examiner also made several suggestions regarding technical changes to the language of the claims. The claims have been amended to incorporate the suggested changes.

Claims 3, 7-15 and 39 have been canceled. Claims 1, 4, 16-19, 23-26, 30-33, 35 and 38 have been amended. The amendments are supported throughout the application, e.g., at page 6, lines 14-21; and pages 8-10. New claims 40-43 have been added and are supported, e.g., at page 8, lines 21-23; and page 9, lines 12-14. No new matter has been added.

Upon entry of this amendment, claims 1, 2, 4-6,16-38 and 40-43 will be pending.

The present claims relate to methods that involve evaluating PKC activity in monocytes as a proxy for: PKC activity in cardiovascular tissue (claims 1, 2, 4-6); the extent, stage, or severity of a cardiovascular complication of diabetes (claims 16-22); or the effect of a treatment or test compound on a cardiovascular complication of diabetes (claims 23-37). The methods of claims 38 and 40-43 involve using monocyte PKC activity as a proxy for age or the effects of test compounds on aging.

Rejections Under 35 U.S.C. §102

Claims 1-15 are rejected as anticipated by Ceolotto. Ceolotto discloses that an increase in plasma glucose level in diabetic subjects correlates with increased monocyte membrane PKC activity. This rejection has been met, in part, by canceling claims 7-15. With regard to pending claims 1, 2 and 4-6, the rejection is respectfully traversed.

Ceolotto measured monocyte PKC activity and plasma glucose in 19 subjects diagnosed with Type 2 diabetes. Ceolotto concludes that "monocytes are a useful cellular model to detect hyperglycemia-induced changes in PKC protein content and activity." Thus, Ceolotto describes a correlation between monocyte PKC activity and blood glucose, nothing more. Ceolotto does not disclose a correlation between monocyte PKC activity and PKC activity in a cardiovascular tissue.

The Examiner referred to some statements in Ceolotto, where Ceolotto speculates that PKC response in monocytes "may mirror that of vascular cells" (page 1316, 2d column, emphasis added); "may parallel those in other types of cells, such as vascular cells" (page 1321, 2d column, emphasis added); and "may be relevant to the study of development of diabetic complications and atherosclerosis" (page 1321, 2d column, emphasis added). Ceolotto also states that "circulating monocytes might represent a potentially suitable cell model to detect modifications in kinase activities in response to changes of the metabolic environment" (page 1316, 2d column, emphasis added). However, Applicant submits that all of these are no more than speculative statements. A statement that something "may" happen can not be read as a teaching that it does happen or that it will happen if one performs an experiment. Furthermore, other than this purely speculative statement, Ceolotto provides no data or teaching that monocyte PKC activity correlates with PKC activity in any vascular tissue. Thus, Ceolotto does not anticipate claims 1, 2 and 4-6. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Rejections Under 35 U.S.C. §103

Claims 16-39 are rejected as obvious over Ceolotto. The Examiner provides the following grounds for the rejection:

> Ceolotto . . .teaches on page 1316 column 2, assessing PKC activity in monocytes may mirror that of vascular cells, the relation between hyperglycemia and PKC activity. On page 1318 column 2, monocytes are a useful model to detect hyperglycemia induced changes in PKC protein content and activity. PKC activity in monocytes may mirror those in other types of cells such as vascular cells. Glucose induced alteration in monocyte PKC kinase activity may be relevant to the study of development of diabetic complications and atherosclerosis.
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> Claims 16-22 differ from Ceolotto in that they specify evaluating extent, stage, or severity of a disorder. Claims 23-29 differ in that they are directed to evaluating effect of treatment. Claims 30-39 are directed to identifying a compound for treating.
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> It would have been obvious to one of ordinary skill in the art at the time the invention was made to diagnose, treat, evaluate treating, identify compounds to treat a disorder after comprehending the mechanism of action of the disorder.

Ceolotto discloses a relationship between PKC activity in monocytes and hyperglycemic disorders and sequelae.

Claim 39 has been canceled. The rejection has been met by substantially narrowing claims 16-37 to recite "a cardiovascular complication of diabetes" rather than "a PKC related disorder" and to delete the phrase "an aging related disorder" in claim 38. The presently claimed methods involve evaluating PKC activity in monocytes as a proxy for the extent, stage, or severity of a cardiovascular complication of diabetes (claims 16-22); the effect of a treatment or test compound on a cardiovascular complication of diabetes (claims 23-37); or the effects of test compounds on aging (claim 38).

As discussed above, Ceolotto only discloses a correlation between monocyte PKC activity and blood glucose level. Ceoletto does not disclose or suggest a correlation between monocyte PKC activity and any cardiovascular complication of diabetes, much less a correlation with severity or stage of a cardiovascular complication, as recited in claims 16-37. Indeed, Ceolotto notes that the type 2 diabetic subjects of the study were free of peripheral vascular disease, free of atherosclerotic cardiovascular disease and "[p]atients with proliferative retinopathy or significant renal impairment [i.e., nephropathy] were also excluded" from the subject population (see Ceolotto, paragraph bridging pages 1316-1317 and page 1317, first full paragraph of first column). Therefore, Ceolotto does not teach or suggest anything about monocyte PKC activity as it relates to the severity or stage of cardiovascular complications of diabetes, much less the specific cardiovascular complications recited in the dependent claims, because patients with these complications were not even part of Ceolottos' study. Certainly, Ceolotto's statement that monocytes PKC activity "may be relevant to the study of development of diabetic complications" does not suggest a diagnostic correlation.

With regard to claim 38, the rejection has been met by deleting the reference to "aging related disorders." The presently claimed methods involve using monocyte PKC activity as a proxy for the effects of test compounds on aging. Ceolotto does not mention age or aging at all, much less disclose or suggest a correlation between monocyte PKC activity and aging.

In light of the foregoing, Applicant submits that the present claims are non-obvious over Ceoletto. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1-39 are rejected "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." The Examiner argues as follows:

> No useful data is presented in table form. Fig. 1 shows some correlation between blood glucose level, presumably in human blood serum, and PKC activity in monocytes. Fig. 2 shows a lack of any identifiable correlation between HbA1c level and PKC activity. Fig. 3 suggests there is a correlation between PKC activity in something and diabetic retinopathy. Fig. 4 suggests there is a correlation between PKC activity in something and diabetic nephropathy.
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> To claim treating humans for a large variety of disorders well know to be difficult to treat by administering something is not enabled by the specification as originally filed. No correlation is seen between PKC activity in monocytes and any other tissue. No correlation is seen between PKC activity in monocytes and "a PKC related disorder". No compound is identified for treatment of anything, most particularly aging. No treatment of anything is evaluated by determining PKC activity of anything in any living thing.

This rejection has been met, in part, by narrowing the claims to recite evaluating PKC activity in monocytes as a proxy for: PKC activity in cardiovascular tissue (claims 1, 2, 4-6); the extent, stage, or severity of a cardiovascular complication of diabetes (claims 16-22); the effect of a treatment or test compound on a cardiovascular complication of diabetes (claims 23-37); or the effects of a test compound on aging (claims 38 and 39). Insofar as the rejection may be applied to the presently pending claims, the specific grounds for the rejection are traversed for the following reasons.

Applicant's data and guidance, although not presented in table form, is presented throughout the application, for example, in the figures and the discussion of the figures and experiments in the specification. For example, at page 8, lines 8-18, Applicant describes experiments in which an increase in each of heart, aorta and retina PKC activity was found to correlate with a very similar percent increase in monocyte PKC activity in an STZ-induced diabetic rat model. Thus, Applicants have clearly shown that a correlation exists between PKC

activity in monocyte and cardiovascular tissue. Accordingly, there is no reason to think that the methods of claims 1, 2 and 4-6 would not work as claimed.

In addition, Applicants provide detailed guidance relating to the correlation between monocyte PKC activity and severity of cardiovascular diabetic complications, e.g., diabetic nephropathy or diabetic retinopathy, in humans. In particular, Applicants provide the following results of human studies at page 8, line 24 to page 9, line 8, as follows.

> PKC activity in human monocytes was significantly increased by 62% in patients with diabetes compared to control subjects ($p<0.05$). PKC activity in human mononuclear cells was significantly correlated with blood glucose level ($R = 0.462$, $R^2 = 0.214$, $p < 0.001$) (Figure 1), and with levels of glycosylated hemoglobin (HbA1c) in the subjects ($R = 0.547$, $R^2 = 0.300$, $p < 0.001$) (Figure 2).
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> To examine relationships between PKC activity and diabetic complications, the diabetic patients were divided into groups according to the severity of complications. PKC activity increased with severity of diabetic retinopathy (non-DR; 134 ± 24, non-proliferative-DR; 162 ± 25, proliferative DR; 184 ± 37) (Figure 3). Also, PKC activity in the group of diabetic patients with proliferative retinopathy was significantly higher than that in the group of patients without retinopathy ($p < 0.001$).
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> Patients were also classified according to severity of diabetic nephropathy. PKC activity was increased in correlation with the severity of the nephropathy (without microalbumiuria; 145 ± 35, with microalbumiuria; 164 ± 31, with proteinuria and/or renal failure; 192 ± 19), and a significant difference was identified between the diabetic group without microalbumiuria and the group with proteinuria and/or renal failure ($p = 0.003$) (Figure 4). (Emphasis added.)

The above quoted passage of Applicant's specification describes two working examples of the claimed methods, in particular of claims 16-22. Applicant's data clearly shows that monocyte PKC activity increases with increasing severity of two representative cardiovascular diabetic complications: diabetic retinopathy and diabetic nephropathy. Statistically significant differences in monocyte PKC activity are present in patients with the most severe stage of either complication compared to diabetic controls. Thus, Applicants have clearly shown that a correlation exists between PKC activity in monocytes and extent, stage or severity of cardiovascular diabetic complications. Thus, given the guidance and data presented in

Applicant's specification, combined with the level of skill in the art, a skilled artisan could perform the methods of claims 16-37 without undue experimentation.

Moreover, the above quoted passage makes it clear that the PKC activity measured in Figures 1-4 is monocyte PKC activity in human patients. Additional confirmation of this is provided at page 9, lines 29-31, which states that "PKC activity in mononuclear cells of human subjects was . . . . associated with the severity of diabetic complications" (emphasis added). In light of Applicant's disclosure, and in particular the above quoted passage, the contents of Figure 3 and 4 are clear. Nonetheless, Applicant agree with the Examiner that the figure descriptions do not explicitly state that it is monocyte PKC activity that is being measured. Thus, Applicant has amended the description of Figures 3 and 4 to clarify that the PKC activity is monocyte PKC activity, as supported, e.g., by the above quoted passages and discussion of the figures in the specification.

In another aspect of the rejection, the Examiner asserts that "treating humans for a large variety of disorders well know to be difficult to treat by administering something is not enabled by the specification." Applicant respectfully submits that enablement of "treating humans" is not necessary to enable the present claims. Applicant notes that none of the presently pending claims are methods of treatment. The only pending claims that recite the term "treatment" at all are claims 23-38. These claims are methods of evaluating the effect of a treatment or methods of screening for a treatment compound. As disclosed in the specification, e.g., at page 3, lines 20-22, methods of evaluating the effect of a treatment can be used to evaluate the effect of an experimental treatment, e.g., an experimental compound, or a known treatment. Screening methods, by their very nature, are to be used with any test compound. Thus, given the guidance in the specification showing, e.g., a correlation between monocyte PKC activity and cardiovascular diabetic complications or aging, the claimed methods can be predicted to work as claimed.

Moreover, the Examiner's statement that "[n]o treatment of anything is evaluated by determining PKC activity of anything in any living thing" is respectfully traversed. The Examiner is directed to page 8, lines 9-18, where Applicant shows that treatment of rats with STZ caused an increase in monocyte PKC activity that correlated with PKC activity in cardiovascular tissues. The increase in monocyte PKC activity due to the STZ-induced diabetes

was then restored to the level of control rats by treatment with insulin. This experiment is a working example of the claimed methods. Accordingly, the present claims are enabled.

In light of the foregoing, Applicant respectfully requests that the rejection be withdrawn.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 30-39 are rejected as indefinite. In particular, the Examiner states:

> [claim 30] is incomplete where a single determination of PKC activity would not be seen to identify a compound. Claim 35 is unclear as to the function of evaluating PKC activity before administration.

Claims 30 and 35 have been amended for clarity to address the Examiner's concerns. In addition, the claims have been amended to incorporate several other suggestions relating to claim language which the Examiner made during the interview. For example, independent claims 1, 16 and 23 were amended to contain an affirmative "correlating" step and to replace the term "evaluating" with the term "determining". Claims 1, 16 and 23 were also amended to recite verb tenses consistently throughout the claims. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection.

Title

The Examiner states that the title of the invention is not aptly descriptive. The title has now been amended to better describe the invention.

Informalities

In addition, the disclosure is objected to for various informalities. To address the Examiner's concerns, the Brief Description of the Drawings has been amended and the underlining at page 7 has been deleted.

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